REMARKS

Claim amendments

Claims 1, 20, 21, 25, 26, 30-32, 36 and 37 have been amended to clarify that "HIF" is hypothalamic inhibitory factor. Support for the amendment can be found, for example, on page 2, line 7 of the specification.

Claims 11, 21 and 26 have been amended to replace "derived from" with "obtained from". Support for the amendment can be found, for example, on page 6, lines 3 and page 7, lines 3-9 of the specification.

Claims 20, 21, 25 and 37 have been amended to replace "HIF-like inhibitory activity" with "HIF inhibitory activity". Support for the amendment can be found, for example, on page 5, line 4 and page 9, line 27 of the specification.

Claims 20 and 21 have been amended to delete "other than ouabain". Support for the amendment can be found, for example, on page 2, lines 21-23 and page 5, lines 4 and 20 of the specification.

No new matter has been added.

Restriction/Election

The Examiner notes Applicant's election of the claims of Group I (Claims 1-32) and the species of detection of RB^+ uptake in liposomes (Claims 1-19 and 32).

Upon further review of the Restriction Requirement mailed from the U.S. PTO, Applicant notes that with the election of Group I, the Examiner had required a further species election of the an ATPase as listed in Claims 9-11 and 15-18, and if an ATPase from a target cell is elected, then a disorder as listed in Claims 12-14, 22-24, 27 and 28 must also be elected. However, Applicant did not elect a species from these groups, and apologizes for the oversight.

Since the Examiner has examined the application without this election, it appears as if the additional species election is moot. However, if the additional species election still applies, Applicant elects rodent ATPase. Since an ATPase isolated from a target cell was not elected, it is Applicant's understanding that it is not necessary to elect a disorder as listed in Claims 12-14, 22-24, 27 and 28. Claims readable on the additional species election are Claims 1-8, 15, 16 and

32.

Applicant respectfully requests that the Examiner confirm whether the additional species election is moot or still applies to the subject application.

Rejection of Claims 1-19 and 32 under 35 U.S.C. §112, second paragraph

Claims 1-19 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 2).

Specifically, the Examiner states that "Claims 1-19 and 32 are indefinite because of use of the term 'HIF'" and suggests fully spelling out the word in the claims.

Independent Claims 1, 20, 21, 25, 26 and 30-32 have been amended to clarify that "HIF" is hypothalamic inhibitiory factor in accordance with the Examiner's suggestion.

The Examiner further states that Claims 12-14 are indefinite "because of the term 'derived from'" and suggests replacing the term with "is obtained from". (Office Action, page 2).

The phrase "derived from" was found in Claims 11, 21 and 26 which have been amended in accordance with the Examiner's suggestion.

Finally the Examiner notes that Claims 13 and 14 are rejected for "being dependent on a rejected claim" (Office Action, page 3).

Applicants are confused by this rejection. Claims 13 and 14 depend from Claim 12. As noted above, the term "derived from" was found in Claims 11, 21 and 26, not Claim 12. Thus, Applicants assume that Claims 13 and 14 were improperly rejected. Applicants respectfully request clarification if this assumption is incorrect.

The claims, particularly as amended, particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Rejection of Claims 1, 4, 5, 8-10, 15, 16 and 19 under 35 U.S.C. §103(a)

Claims 1, 4, 5, 8-10, 15, 16 and 19 have been rejected under 35 U.S.C. §103(a) "as being unpatentable over Anner *et al.* (Am. J. Physiol. 258, F144-153 (1990) in view of Haupert, Jr. (The Sodium Pump, Steinkopff & Darmstadt (pub), N.Y. pp732-742 (1994)" (Office Action, page 3). The Examiner states that Anner *et al.* teach inhibition of Na^+-K^+-ATPase by HIF "using a miniaturized, two-sided test system containing ATP-filled liposomes having dispersed,

randomly oriented renal Na^+-K^+-ATPase molecules" (Office Action, page 3). The Examiner further states that Anner *et al.* teach that "the inhibition was monitored by the uptake of $^{86}RB^+$-containing liposomes, which are separated by Sephadex G-50 column"; that "HIF is isolated from bovine hypothalamus" and that "the inhibition of inside-out-oriented Na^+-K^+-ATPase (ISO) by other compounds such as digoxin has also been shown" (Office Action, page 3). The Examiner cites Haupert, Jr. as teaching that "in search of endogenous inhibitor Na^+-K^+-ATPase, it is found that HIF inhibition on Na^+-K^+-ATPase incorporated into liposomes is reversible, which can be monitored by the assay system of Anner *et al.*, and the inhibitions of HIF and Ouabain on isoenzymes of the Na^+-K^+-ATPase and Ouabain-resistant Na^+-K^+-ATPase are compared, where the existence of isoforms showing different sensitivities to ouabain and HIF, and the Ouabain-resistant α_1 isoform is obtained from rat kidney" (Office Action, pages 3-4). It is the Examiner's opinion that at the time of the invention, "it would have been obvious to one of ordinary skill in the art to combine the two references to screen a compound for HIF inhibitory activity of Ouabain-resistant Na^+-K^+-ATPase as indicated by Haupert, Jr. using the assay system indicated by Anner *et al.* because using Ouabain-resistant Na^+-K^+-ATPase in the assay can provide a method to identify an inhibitor that has target organ selectivity, which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made" (Office Action, page 4).

Applicants respectfully disagree. Anner *et al.* used a "miniaturized functional test system based on ATP-filled liposomes containing dispersed, reconstituted renal Na^+-K^+-ATPase molecules in symmetric orientation for analyzing some properties of a low-molecular-weight, stable, nonpeptidic Na^+-K^+-ATPase inhibitor isolated from bovine hypothalamus:, *i.e.*, HIF (Anner *et al.*, page F144, column 2). As the Examiner notes, Anner *et al.* do not teach "monitoring the inhibition of the ouabain-resistant Na^+-K^+-ATPase" (Office Action, page 3). Anner *et al.* also do not teach or suggest substances other than ouabain or HIF having HIF inhibitory activity.

Haupert reviewed "the biological properties and structural characteristics which distinguish the pharmacological inhibitor, ouabain, from the putative physiological mammalian analogue, HIF" (Haupert, page 732, column 2). Haupert teaches that "[u]sing the active influx of $^{86}Rb^+$ as a measure of Na^+ pump activity in the ***intact renal cell***, HIF was found to completely

inhibit the pump activity . . ." and that "the HIF-induced inhibition was rapidly reversible . . . (Haupert, page 733, column 2). Haupert does not teach that this occurred using Na^+-K^+-ATPase incorporated into liposomes. Haupert also does not discuss substances other than ouabain or HIF having HIF inhibitory activity. In discussing the effects of HIF on Na^+/K^+-ATPase isoenzymes and on Na^+/K^+-ATPase of ouabain-resistant species, Haupert teaches that:

> While the existence of isoforms showing different sensitivities to ouabain and HIF (albeit of a widely different magnitude) provides a ***seed of rationale for target organ selectivity, it is clear that such selectivity in any eventual endogenous regulation must be more complex*** since tissues expressing the same α_1 isoform across species ***show widely different sensitivities to ouabain***. Thus canine renal Na^+/K^+-ATPase, α_1, is ouabain sensitive, but rat renal Na^+/K^+-ATPase, also α_1, is highly resistant, as noted. Consistent with functional differences concerning isoform sensitivities, ***HIF was also shown to not distinguish between ouabain-sensitive and ouabain-resistant renal Na^+/K^+-ATPase forms***. This finding may be important since it is further evidence that ***HIF interacts with target organ enzymes differently than ouabain***, and may consequently have a different regulatory role *in vivo* (Haupert, page 735, column 2, emphasis added).

Haupert, Jr. clearly teaches that regulation of target organ selectivity by HIF, the endogenous, mammalian analogue of ouabain, is more complex than the regulation of target organ sensitivity by ouabain since, unlike ouabain, HIF does not distinguish between ouabain-sensitive and ouabain-resistant Na^+-K^+-ATPases.

Based on the teaching of Haupert, Jr. one of skill in the art would clearly not be motivated to use the assay system of Anner *et al.* with a ouabain-resistant Na^+-K^+-ATPase to screen for an HIF-like inhibitor having target organ selectivity since Haupert, Jr. teaches that regulation of target organ selectivity by HIF is more complex than the regulation of target organ sensitivity by ouabain. Thus, Haupert, Jr. teaches away from using the assay system of Anner *et al.* with a ouabain-resistant Na^+-K^+-ATPase to screen a test substance for HIF inhibitory activity.

The combined teaching of Anner *et al.* in view of Haupert, Jr. does not render obvious Applicant's claimed invention.

Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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